Comments of the American Chemistry Council's Ethylene Oxide Panel (ACC) on the Draft Charge to the Science Advisory Board for the IRIS Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Revised External Review Draft – August 2014)

September 23, 2014

ACC commented in 2013 on a previous version of the assessment you are currently reviewing. Prior to the November, 2014 CAAC meeting, these comments will be submitted for your review of the current draft along with additional information on key points made in the current draft. In Appendix L, EPA responds to public comments with rationales for decisions made. However, in a few cases, it is not clear to us that EPA has been sufficiently responsive. We are pleased to see that a general charge question has been included which asks the CAAC to comment on these responses. Our comments now focus on the six questions proposed for this review.

Charge Questions:

The first four charge questions (1-4) pertain to the review of those sections of the draft assessment that deal with the exposure-response modeling of the epidemiologic data and development of cancer risk estimates. The final two questions (5-6) are more general and refer to the accuracy, objectivity, and transparency of the revised draft.

Questions 1-4:

In general, these charge questions seek comment on the methods, results, and conclusions from EPA's cancer dose-response assessment of the epidemiologic data (Chapter 4, omitting Section 4.2, and Appendix D) in terms of the extent to which they are clearly and transparently described and technically/scientifically adequate for the purposes of estimating risk for lymphoid cancer and for breast cancer. The questions also address how well the 2007 SAB recommendations and public comments on these topics (Chapter 4 and Issue 2 of Appendix H) were addressed. In particular, please address the following issues:

1. **Exposure lagging.** Exposure-response modeling was conducted separately for lymphohematopoietic cancer mortality, with attention to lymphoid cancer, and breast cancer incidence and mortality. In the Cox proportional hazards models, a lag period was used to represent an interval before cancer death (or diagnosis, in the case of breast cancer incidence), or the end of follow-up, during which any exposure was disregarded because it was not considered relevant for the development of the cancer outcome observed. The lag period for each of the different cancer types was selected empirically based on statistical fit.

These exposure lag periods were included in EPA's exposure-response analyses using other model forms for the derivation of cancer risk estimates. Please comment on whether the use of lagged exposure estimates in the derivation of cancer risk estimates and the selection of the lag periods used are clearly described and scientifically appropriate.

ACC recommends the following addition to the charge question:

Please describe any other approaches for exposure-response modeling that should be considered.

ACC recommends an additional charge question:

One of the default assumptions in EPA's cancer risk paradigm is that all exposures contribute to cancer risk. In the modeling of epidemiology data for ethylene oxide, some exposure information is discarded under an assumption that it does not contribute to the observed cancer response (e.g., exposure lagged). For the grouping of lymphohematopoietic cancers, a 15-year lag was assumed, a duration based purely upon empirical support (i.e., using this lag assumption results in a significant trend with exposure). However, latencies for individual cancer types vary, ranging from 2-10 years for lymphomas, and from 1.5-15 years for leukemias (CDC, 2013). Furthermore, with a 15-year lag, it is assumed that ethylene oxide exposures affect an early stage of the disease (i.e., induction), while any effects of ethylene oxide exposure on later stages (progression) are potentially ignored. Please comment on the appropriateness of applying a single, long lag value for this diverse group of cancers.

2. **Breast cancer incidence – model selection.** As discussed in the Background section, a number of different statistical models were examined and a number of considerations were used in the selection of the preferred model (the two-piece linear spline model), which was selected for the derivation both of estimates of risk in the range of the occupational exposures of concern and of estimates of risk at exposures well below the occupational range of concern.

   2.a. Please comment on whether the considerations used for model selection and their application in the selection of preferred exposure-response models for breast cancer incidence for the purposes of estimating low-exposure cancer risks (Section 4.1.2.3) and the cancer risks from occupational exposures (Section 4.7) are clearly and transparently described and scientifically appropriate.

ACC recommends the following addition to the charge question:

Are there any modifications you would recommend to improve the approach?

2.b. For the (low-exposure) unit risk estimates, EPA presents an estimate from the preferred model as well as a range of estimates from models considered "reasonable" for that purpose (Sections 4.1.2.3 and 4.5 and Chapter 1). Please comment on whether the rationale provided for defining the "reasonable models" is clearly and transparently described and scientifically appropriate.

2.c. For analyses using a two-piece spline model, please comment on whether the method used to identify knots (Section 4.1.2.3 and Appendix D) is transparently described and scientifically appropriate.

ACC recommends an additional charge question:

A two-piece linear spline has not been applied to estimate cancer potency for other chemicals. The identification of knots used in the spline analysis is based on empirical support. Please comment on the appropriateness of the spline analyses.

3. Lymphoid cancer – model selection. EPA attempted to develop additional models of the continuous data for lymphoid cancer mortality, as recommended by the SAB (SAB, 2007), but was unable to obtain suitable models for the purposes of estimating a (low-exposure) unit risk; thus, EPA used a linear regression of the categorical results as the preferred model for derivation of the unit risk estimate for lymphoid cancer (Section 4.1.1). For the lymphoid cancer risks from occupational exposures, a model of the continuous data was selected as the preferred model (Section 4.7).

3.a. Please comment on EPA's rationale for its use of the linear regression of the categorical results as the preferred model for the derivation of the (low-exposure) unit risk estimate for lymphoid cancer (Section 4.1.1.2).

ACC recommends the following additions to the charge question:

Please comment on EPA's method of implementing their linear regression of the categorical results and EPA's rejection (discussed in EPA's Appendix J.3.1) of the modeling recommendations in Valdez-Flores and Sielken (2013).

Consistent with the SAB recommendation not to model categorical results, please suggest other approaches that may be appropriate.

3.b. Please comment on whether the considerations used for model selection and their application in the selection of the preferred exposure-response models for lymphoid cancer for the purposes of estimating low-exposure cancer risks (Section 4.1.1.2) and the cancer risks from occupational exposures (Section 4.7) are clearly and transparently described and scientifically appropriate.

ACC recommends the following addition to the charge question:

Please also comment on whether the considerations used for model selection have been appropriately applied.

3.c. EPA used the lymphoid cancer mortality exposure-response models in the lifetable calculations for the derivation of risk estimates for lymphoid cancer incidence. Please comment on whether the approach used for deriving these risk estimates for lymphoid cancer incidence and the rationale for using this approach are transparently described and scientifically appropriate (Section 4.1.1.3).

ACC recommends an additional charge question:

The preferred approach to selecting relevant mode of action (MOA) is to employ current understanding of the molecular mechanisms involved in the pathogenesis of specific lymphoid cancers of interest as the basis for selection. Does the current hazard assessment, which assumes a mutagenic MOA for ethylene oxide in developing a preferred model for deriving risk estimates for lymphoid cancers, adequately address science that supports different MOAs that are independent of mutagenesis for specific lymphoid cancers?

4. **Uncertainty in the cancer risk estimates.** Please comment on whether the qualitative discussions of uncertainty (Sections 4.1.4, 4.5, and 4.7 and Chapter 1) are clear, objective and scientifically appropriate.

ACC recommends the following additions to the charge question:

Have uncertainties of the NIOSH exposure assessment been adequately discussed given the absence of data prior to 1979?

Have uncertainties of the NIOSH breast cancer incidence study related to potential selection bias been adequately considered?

Questions 5-6:

5. Please comment on the accuracy, objectivity, and transparency of the revised draft assessment, with particular emphasis on the following sections, which are either new or substantially revised since the 2007 external peer review:

   - Section 3.3.3 and Appendix C (genotoxicity)

   - Appendix H (EPA's responses to the 2007 external review comments), in particular the responses to the comments on endogenous EtO (p. H-4), a nonlinear approach (p. H-13 to H-17), and the cancer hazard characterization (p. H-3).

ACC recommends the following addition to the charge question:

Please comment on the transparency of presenting the epidemiology evidence. Are key details of the findings of the NIOSH breast cancer study included in summary table (Table 3-2)? Should negative findings be included? Should overall SMR and SIR be included?

ACC recommends additional charge questions:

The unit risk calculation for ethylene oxide is a multi-step process, with a range of options available at each step. For each of these steps, please consider:

- ***Are there viable alternatives to the option selected by EPA?***

- ***Is EPA's decision supported by MOA and underlying biological considerations?***

- ***Has the impact of alternative options on resulting unit risk been presented in a transparent manner?***

Ethylene oxide's genotoxicity profile should be presented in a manner that facilitates a determination of a DNA-reactive mutagenic MOA for cancer induction. Modern MOA assessments employ key events as an organizing principle, with a demonstration of one or more pro-mutagenic DNA adducts in the target tissue for specific tumors as the initial key event. The identification of mutations consistent with the adduct profile (molecular mutation spectrum), again in the target tissue, constitutes a later key event and provides confidence in the MOA. The genotoxicity data should be organized in this manner for each tumor attributed to ethylene oxide as it is recognized that different tumors caused by the same agent may have different MOAs, and MOAs may be complex. The decision as to whether to employ both linear and non-linear extrapolations for risk assessment will depend on the outcome of this exercise. How well is it demonstrated that a direct, DNA reactive mutagenic MOA is the only MOA for all tumors attributed to ethylene oxide?

6. Please comment on the completeness and clarity of the appendix describing major new studies published since the first external review draft but not included in the revised assessment (Appendix J) and on the conclusion presented in that appendix that the inclusion of these new studies would not substantially alter the hazard or quantitative findings of the assessment.

7. EPA solicited public comments on a July 2013 public comment draft of the IRIS carcinogenicity assessment of EtO and has revised the assessment to respond to the scientific issues raised in the comments. A summary of the major public comments and EPA's responses are provided in Appendix L. Has EPA adequately addressed the scientific issues raised in the public comments? For example, please comment on EPA's explanations for (i) its use of the lymphoid cancer grouping and (ii) combining unit risk estimates derived separately for the independent cancer types of lymphoid cancer and breast cancer to develop a total cancer unit risk estimate.

ACC recommends the following modification to charge question #7:

~~Has EPA adequately addressed the scientific issues raised in the public comments?~~ ***Please consider in your review whether there are scientific issues that were raised by the public as described in Appendix L that may not have been adequately addressed by EPA Are the responses scientifically robust?*** For example, please comment on EPA's explanations for (i) its use of the lymphoid cancer grouping and (ii) combining unit risk estimates derived separately for the independent cancer types of lymphoid cancer and breast cancer to develop a total cancer unit risk estimate.

References

SAB (Science Advisory Board). (2007). Review of Office of Research and Development (ORD) draft assessment entitled "Evaluation of the carcinogenicity of ethylene oxide". Washington, DC: Science Advisory Board, U.S. Environmental Protection Agency. http://yosemite.epa.gov/sab/sabproduct.nsf/368203f97a15308a852574ba005bbd01/5D661BC118B527A3852573B80068C97B/$File/EPA-SAB-08-004-unsigned.pdf

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Valdez-Flores, C., Sielken R.L. Jr. (2013). Misinterpretation of categorical rate ratios and inappropriate exposure-response model fitting can lead to biased estimates of risk: ethylene oxide case study. Regul Toxicol Pharmacol 67(2): 206-214.